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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte CLAUDIO BUCOLO, MELINA G. CRO,
ADRIANA L. A. MALTESE, and DHARMENDRA M. JANI

Appeal 2010-001259
Application 10/812,551
Technology Center 1600

Before CAROL A. SPIEGEL, LORA M. GREEN, and
MELANIE L. McCOLLUM, *Administrative Patent Judges*.

McCOLLUM, *Administrative Patent Judge*.

DECISION ON APPEAL[1]

This is an appeal under 35 U.S.C. § 134 involving claims to a viscoelastic composition. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the "MAIL DATE" (paper delivery mode) or the "NOTIFICATION DATE" (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

STATEMENT OF THE CASE

Claims 1, 6-11, 20, 22, 25-28, and 47 are on appeal. Claims 15-17 are also pending but have been withdrawn from consideration by the Examiner. (App. Br. 3.) We will focus on claims 1, 7, 11, 22, and 47, which read as follows:

1. A viscoelastic composition comprising a viscoelastic polymer comprising:

a mixture of hyaluronic acid and/or salts thereof and hydroxypropyl-methylcellulose, wherein the concentration of hyaluronic acid and/or salts thereof is a minimum of about 0.1%w/v and a maximum of about 6%w/v and the concentration of hydroxypropylmethylcellulose is a minimum of about 0.05%w/v and a maximum of about 5%w/v, based upon the total volume of the viscoelastic composition;

tris[hydroxymethyl]aminomethane at a maximum of about 50mM and a minimum of about 0.1mM based upon the total weight of the viscoelastic composition; and

a hexahydric alcohol.

7. The composition of claim 1, wherein the hexahydridic [sic] alcohol is sorbitol.

11. The composition of claim 1, wherein the composition possesses a minimum quenching of about 45% as quantified by a TBA-MDA complex.

22. The composition of claim 1, wherein the average molecular weight of the hydroxypropylmethylcellulose is a minimum of about 10 kD and a maximum of about 120 kD.

47. A viscoelastic composition comprising:

a viscoelastic polymer comprising a mixture of hyaluronic acid and/or salts thereof and hydroxypropylmethylcellulose, wherein the concentration of hyaluronic acid and/or salts thereof is a minimum of 0.1%w/v and a maximum of 6%w/v and the concentration of hydroxypropylmethylcellulose is a minimum of 0.05%w/v and a maximum of 5%w/v, based upon the total volume of the viscoelastic composition;

tris[hydroxymethyl]aminomethane at a maximum of about 50mM and a minimum of about 0.1mM based upon the total weight of the viscoelastic composition; and

a hexahydric alcohol selected from mannitol or sorbitol;

said viscoelastic composition having a zero-shear viscosity from $6 \cdot 10^4$ cps to $4 \cdot 10^6$ cps, and a high-shear viscosity from 500 cps to 2000 cps.

Claims 1, 6-11, 25-28, and 47 stand rejected under 35 U.S.C. § 103(a) as obvious over Singh et al. (US 2003/0232089 A1, Dec. 18, 2003) in view of Olejnik et al. (US 5,597,559, Jan. 28, 1997) and Gohzu et al. (US 5,013,445, May 7, 1991) (Ans. 3).

Claim 20 stands rejected under 35 U.S.C. § 103(a) as obvious over Singh in view of Olejnik, Gohzu, and Cantoro (US 5,770,628, Jun. 23, 1998) (Ans. 6).

Claim 22 stands rejected under 35 U.S.C. § 103(a) as obvious over Singh in view of Olejnik, Gohzu, and Katz (US 4,287,175, Sep. 1, 1981) (Ans. 6).

I

The Examiner relies on Singh for teaching "trishydroxymethylaminomethane as a buffering component . . . for ophthalmic gum compositions . . . where the composition can include hyaluronic acid . . . and hydroxypropylmethyl cellulose (HPMC)" (Ans. 3). The Examiner finds that the "working examples teach the combination of 0.5% HPMC and 0.5% Scleroglucan" and that the "addition of a tonicity modifier is also taught" (*id.*).

The Examiner relies on Olejnik for teaching that "tonicity adjusting agents known in the art include mannitol and sorbitol" (*id.*). The Examiner relies on Gohzu for teaching that "trishydroxymethylaminomethane is

known to be a buffering agent where at an amount between 5-100 mM, the composition generally achieves a pH of from 6.0 to 7.5" (*id.* at 4).

The Examiner concludes that it would be obvious "to substitute the disclosed 'gum' compounds, such as hyaluronic acid for Scleroglucan (or in addition to Scleroglucan) in the working example ID 21 where the prior art discloses the ability to substitute the same and the benefit of adjusting the viscosity by doing so"; that the "addition of a tonicity adjusting agent, such as the common tonicity agents of Olejn[i]k, would be obvious where the primary reference suggests the same"; and that, "where the addition of buffering agents is taught, the amount of buffering agent would be a matter of routine optimization based on the desire to achieve a physiological pH similar to that disclosed in Gohzu" (*id.*).

Issues

Does a preponderance of the evidence of record support the Examiner's conclusion that Singh, Olejnik, and Gohzu suggest a viscoelastic composition comprising hyaluronic acid, HPMC, tris[hydroxymethyl]amino-methane, and a hexahydric alcohol?

Does a preponderance of the evidence of record support the Examiner's conclusion that it would have been obvious to include sorbitol as the hexahydric alcohol?

Does a preponderance of the evidence of record support the Examiner's conclusion that Singh, Olejnik, and Gohzu suggest a composition that possesses a minimum quenching of about 45% as quantified by the TBA-MDA complex?

Does a preponderance of the evidence of record support the Examiner's conclusion that Singh, Olejnik, and Gohzu suggest a composition that has the shear viscosities recited in claim 47?

Findings of Fact

1. Singh states that "[m]any of the marketed ophthalmic formulations currently use the polymers hydroxypropyl methylcellulose [HPMC], hydroxyethyl cellulose, and polyvinyl alcohol to increase the viscosity of the formulation" (Singh ¶ [0005]).

2. Singh discloses "a pharmaceutical composition suitable for topical administration to an eye, comprising an active agent and a novel gum system" (*id.* at ¶ [0013]).

3. Singh also discloses:

> The term "gum" . . . refers to any synthetic polymer, natural polysaccharide, or derivatized natural polysaccharide that is ophthalmically compatible and that increases the viscosity of a solution sufficiently to increase the viscosity of the solution in which it is found or to transform a drop of the solution into a semi-solid or gelatinous state after administration to an eye of a warm-blooded mammal. . . . Examples of natural polysaccharide gums include, but are not limited to, . . . scleroglucan, hyaluronic acid. . . .

(*Id.* at ¶ [0025].)

4. In addition, Singh discloses that the "combinations of gums of the present invention produce unexpected advantages over individual gums" (*id.* at ¶ [0041]).

5. Singh also discloses:

> [S]pecific combinations of gums can be selected to obtain specific viscosity or gelling characteristics. The nonionic gums (e.g., . . . Scleroglucan) do not show significant changes in

> rheological behavior when in contact with artificial tear fluid ("ATF"). The anionic gums . . . in contrast show a decrease in viscosity when mixed with ATF. . . . [I]n general, an anionic gum is preferably combined with a neutral gum since the combination modulates the loss of viscosity of the two individuals.

(*Id.* at ¶ [0042].)

6. In addition, Singh discloses that the "composition preferably further includes at least one agent that improves ocular tolerance, such as aloe vera gel, a buffering agent, and a tonicity modifier" (*id.* at ¶ [0059]).

7. Singh also discloses that the "composition optionally further includes at least one ophthalmically acceptable salt in an amount required to bring osmolality of the composition into an ophthalmically acceptable range. . . . Other solutes suitable for adjustment of osmolality include sugars, for example dextrose, man[n]itol, xylitol, and sucrose." (*Id.* at ¶ [0093].)

8. In addition, Singh discloses that the composition "optionally further includes at least one ophthalmically acceptable pH adjusting agent and/or buffer, including . . . a base such as . . . tris-hydroxymethylamino-methane. . . . Such an acid, base and/or buffer is preferably included in an amount required to maintain pH of the composition in an ophthalmically acceptable range." (*Id.* at ¶ [0094].)

9. Singh also discloses that the composition "optionally further comprises an ophthalmically acceptable mucoadhesive polymer. The mucoadhesive polymer is preferably" HPMC. (*Id.* at ¶ [0098].)

10. In addition, Singh discloses a composition (ID 21) comprising 0.5% scleroglucan and 0.5% HPMC and states that it is a "[w]eak viscoelastic fluid" with 3:1 ATF at 35°C (*id.* at ¶ [0139]: Table 5).

11. Olejnik discloses an "ophthalmic formulation includ[ing] (a) . . . a polymer selected from the group consisting of hydroxyalkyl cellulosics and polyalkylene glycols; and (b) a non-ionic tonicity adjusting agent selected from the group consisting of mannitol, sorbitol, dextrose, sucrose, urea, glycerol, and mixtures thereof" (Olejnik, col. 2, ll. 16-21).

12. Appellants have provided evidence that there is a viscoelastic product, named Healon, for use as an ophthalmo-surgical aid, which contains sodium hyaluronate dissolved in physiological sodium chloride phosphate buffer (App. Br. Evidence Appendix).

13. The Specification discloses eight exemplary formulations (Spec. 14-16).

14. The Specification states:

> The processed Formulations 1 to 8 were chromatographed over a C18 column to detect the pink chromogen product (TBA-MDA complex) using an UV-VIS detector at 532 nm. . . . The percentage of production of TBA-MDA complex in Formulations 1 through 8 was compared to the standard solution (control), calculated and shown in Table 2. . . . Each of the formulations containing tris[hydroxymethyl]aminomethane and/or sorbitol had higher free radical quenching than samples without either. Tris[hydroxymethyl]aminomethane and sorbitol individually have free-radical quenching properties. The combination of Tris[hydroxymethyl]aminomethane and sorbitol have the best free-radical quenching properties.

(*Id.* at 17.)

15. Specification Table 2 is reproduced below:

Table 2: Percentage of Quenching of Free-Radical Activity					
Formulations	%w/v HA (mw $1.98x10^6$)	%w/v HPMC (mw $8.6x10^4$)	%w/v Sorbitol	Tris (mM)	% of quenching
1	2.3	0.8	4.4	20	92
2	2	0.8	4.4	20	82
3	2	1.0	4.4	20	80
4	2.3	0.8	4.4	-	90
5	2.3	0.8	-	-	80
6	2.3	0.8	-	20	87.6
7	2.3	-	4.4	20	94
8	-	-	-	-	79
Control	-	-	-	-	0

(*Id.* at 18.)

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). "[I]n a section 103 inquiry, 'the fact that a specific [embodiment] is taught to be preferred is not controlling, since all disclosures of the prior art, including unpreferred embodiments, must be considered.'" *Merck & Co. Inc. v. Biocraft Labs. Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re Lamberti*, 545 F.2d 747, 750 (CCPA 1976)).

> [I]t is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that

> the subject matter shown to be in the prior art does not possess the characteristic relied on.

In re Best, 562 F.2d 1252, 1254-55 (CCPA 1977). "Whether the rejection is based on 'inherency' under 35 U.S.C § 102, on 'prima facie obviousness' under 35 U.S.C § 103, jointly or alternatively, the burden of proof is the same." *Id.* at 1255. "Attorney's argument in a brief cannot take the place of evidence." *In re Pearson*, 494 F.2d 1399, 1405 (CCPA 1974).

Analysis

Singh discloses "a pharmaceutical composition suitable for topical administration to an eye, comprising an active agent and a novel gum system" (Finding of Fact (FF) 2). We recognize that the teachings of Singh encompass a relatively large number of polymer combinations (*see* FF 3-4). However, as pointed out by the Examiner (Ans. 3), Singh exemplifies a composition (ID 21) comprising HPMC and a natural polysaccharide gum, scleroglucan (FF 10 & 3). In addition, Singh lists hyaluronic acid as an additional example of a natural polysaccharide gum (FF 3). Thus, we agree with the Examiner that it would have been prima facie obvious to add hyaluronic acid to ID 21 in place of or in addition to the scleroglucan (Ans. 4).

We also note that Singh exemplifies a composition that is described as a weak viscoelastic fluid (FF 10). Thus, we do not agree that viscoelastic compositions would not have been prima facie obvious based on the disclosures in Singh.

In addition, we recognize that Singh discloses that "an anionic gum is preferably combined with a neutral gum" (FF 5). However, "all disclosures of the prior art, including unpreferred embodiments, must be considered.'"

Merck & Co. Inc. v. Biocraft Labs. Inc., *supra*. Furthermore, as recognized by the Examiner (Ans. 4), claim 1 does not exclude including both hyaluronic acid, which Appellants indicate is anionic (App. Br. 16), and scleroglucan, which is nonionic (FF 5), in addition to HPMC.

Singh also discloses that the composition "optionally further includes at least one ophthalmically acceptable pH adjusting agent and/or buffer, including . . . a base such as . . . tris-hydroxymethylaminomethane" (FF 8). Thus, we agree with the Examiner that it would have been prima facie obvious to include tris-hydroxymethylaminomethane in the composition.

In addition, Singh discloses that the composition may additionally include a tonicity modifier (FF 6). Olejnik discloses including non-ionic tonicity adjusting agents, such as mannitol and sorbitol, in an ophthalmic formulation (FF 11). Thus, we agree with the Examiner that it would have been prima facie obvious to include these non-ionic tonicity adjusting agents, including mannitol and sorbitol, in Singh's composition.

We recognize that Singh discloses that the "composition optionally further includes at least one ophthalmically acceptable salt in an amount required to bring osmolality of the composition into an ophthalmically acceptable range" (FF 7). However, Singh also recognizes that "[o]ther solutes suitable for adjustment of osmolality include sugars" (*id.*). Thus, we do not agree that it would not have been obvious to include sugars, such as mannitol, as taught in both Singh and Olejnik (FF 7 & 11), or sorbitol as taught in Olejnik (FF 11), in Singh's composition.

We also recognize that Appellants have provided evidence that there is a viscoelastic product, named Healon, for use as an ophthalmo-surgical

aid, which contains sodium hyaluronate dissolved in physiological sodium chloride phosphate buffer (FF 12). However, even if this product was known at the time of the present invention, we do not agree that its existence renders the combination of hyaluronic acid with other tonicity modifiers and buffers unobvious.

With regard to claim 11, the Specification discloses a composition comprising hyaluronic acid and HPMC possessing a percentage of quenching of 80% (FF 15: Formulation 5). The Specification also states that "[e]ach of the formulations containing tris[hydroxymethyl]aminomethane and/or sorbitol had higher free radical quenching than samples without either[, t]ris[hydroxymethyl]aminomethane and sorbitol individually hav[ing] free-radical quenching properties" (FF 14), and provides examples showing that this is the case (FF 15). Thus, the evidence of record suggests that a percentage of quenching of about 45% or higher is merely an inherent property of the suggested formulation. Appellants have not shown that this property is not inherent or that it is an unexpected property provided by the combination.

With regard to claim 47, the Examiner finds that the shear-viscosities would be an inherent property of the composition taught by the references as combined (Ans. 4). As the composition suggested by the combination meets the other limitations of claim 47, the ordinary artisan would reasonably expect it to inherently meet the shear viscosity limitation of claim 47. Appellants have not shown that the claimed shear-viscosities are not inherent or that they are unexpected properties provided by the combination.

Instead, Appellants argue "why would one of ordinary skill in the art seek to modify one of Singh's compositions to possess a shear-viscosity recited in the claims if the same person was concerned with a sustained delivery of an ophthalmic drug?" (Reply Br. 4-5.) This argument implies that a composition having the shear-viscosities recited in claim 47 is not taught by Singh and would not be suitable for Singh's compositions, which are intended for topical administration to an eye (FF 2). However, Appellants have not provided evidence that this is the case. In this regard, we note that Singh discloses a viscoelastic composition (FF 10). Thus, we do not agree with Appellants that the Examiner has ignored this claim feature.

Conclusion

A preponderance of the evidence of record supports the Examiner's conclusion that Singh, Olejnik, and Gohzu suggest a viscoelastic composition comprising hyaluronic acid, HPMC, tris[hydroxymethyl]amino-methane, and a hexahydric alcohol. We therefore affirm the obviousness rejection of claim 1. Claims 6, 8-10, and 25-28[2] have not been argued separately and therefore fall with claim 1. 37 C.F.R. § 41.37(c)(1)(vii).

A preponderance of the evidence of record also supports the Examiner's conclusion that it would have been obvious to include sorbitol as

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[2] In the Appeal Brief, Appellants clearly group claims 26 and 27 with claim 1 (App. Br. 14). However, Appellants mention these claims in the Appeal Brief in the context of discussing "Claim 42" [sic, 47] (App. Br. 19) and argue these claims with claim 47 in the Reply Brief (Reply Br. 3-5). To the extent that claims 26 and 27 are considered to have been argued with claim 47, they fall with claim 47.

the hexahydric alcohol. We therefore affirm the obviousness rejection of claim 7.

In addition, a preponderance of the evidence of record supports the Examiner's conclusion that Singh, Olejnik, and Gohzu suggest a composition that possesses a minimum quenching of about 45% as quantified by the TBA-MDA complex. We therefore affirm the obviousness rejection of claim 11.

A preponderance of the evidence of record also supports the Examiner's conclusion that Singh, Olejnik, and Gohzu suggest a composition that has the shear viscosities recited in claim 47. We therefore affirm the obviousness rejection of claim 47.

II

With regard to claim 20, the Examiner relies on Singh, Olejnik, and Gohzu as discussed above (Ans. 6). The Examiner relies on Cantoro for teaching or suggesting the features of claim 20 (*id.*). Appellants argue this claim together with claim 1 (App. Br. 14-17). However, we are unpersuaded by this argument for the reasons discussed above. Therefore, we affirm the obviousness rejection of claim 20.

III

With regard to claim 22, the Examiner relies on Singh, Olejnik, and Gohzu as discussed above (Ans. 6). The Examiner relies on Katz for disclosing "the use of HPMC having a molecular weight of from about 10,000 to 1,000,000 or more, particularly up to about 200,000 and especially about 80,00 to about 125,000 in ophthalmic solutions" (*id.*). The Examiner

concludes that it would be obvious "to use HPMC compounds known to be used in ophthalmic solutions, such as disclosed in Katz" (*id.*).

Issue

Does a preponderance of the evidence of record support the Examiner's conclusion that it would have been obvious to include HPMC having a molecular weight of about 10 kD to about 120 kD?

Findings of Fact

16. Katz discloses HPMC "having a molecular weight of from about 10,000 to 1,000,000 or more, particularly up to about 200,000 and especially about 80,00 [sic, 80,000?] to about 125,000" (Katz, col. 2, ll. 41-44).

17. Olejnik discloses an ophthalmic composition comprising HPMC 90HG 4000 COS, which Appellants state has a reported weight average molecular weight of 89 kD (Olejnik, col. 5, ll. 32-54; App. Br. 20).

Analysis

Appellants argue that "[t]here is no guidance in Singh with regard to a selection of which grade of HPMC one should use, i.e., the low molecular weight form or the high molecular weight form" (App. Br. 20). However, Appellants do not argue that Katz cannot be relied on to teach or suggest the features of claim 22. In addition, Appellants admit that Olejnik, which discloses ophthalmic formulations (FF 11), discloses a composition comprising an HPMC within the range recited in claim 22 (FF 17), lending further support for the Examiner's position that it would have been obvious to use an HPMC within the range recited in claim 22.

Conclusion

A preponderance of the evidence of record supports the Examiner's conclusion that it would have been obvious to include HPMC having a molecular weight of about 10 kD to about 120 kD. We therefore affirm the obviousness rejection of claim 22.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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